



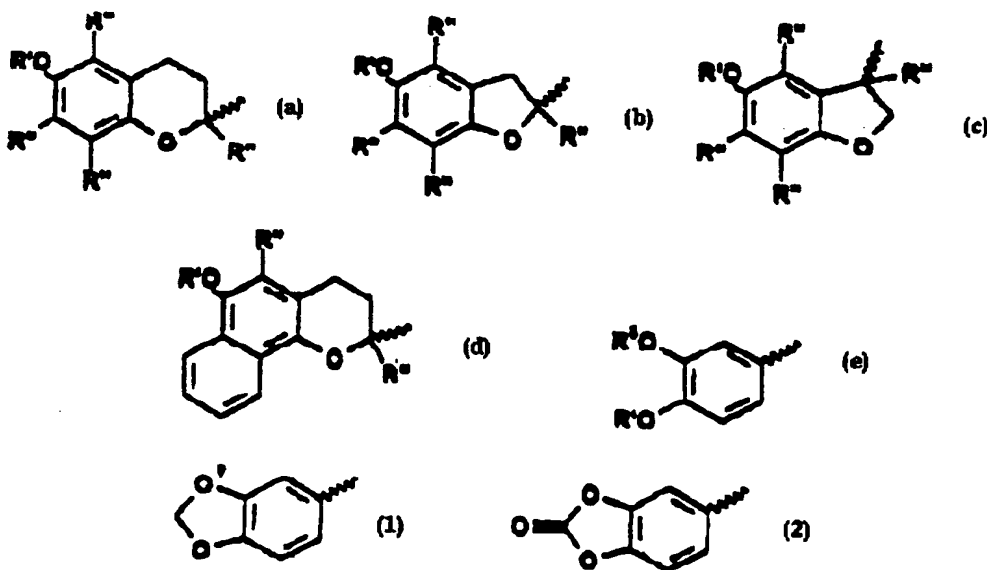
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: ESTERS AND AMIDES OF NON-STEROIDAL ANTI-INFLAMMATORY CARBOXYLIC ACIDS WHICH MAY BE USED AS ANTI-OXIDANTS, 5-LIPOXYGENASE INHIBITORS AND NON-STEROIDAL ANTI-INFLAMMATORY PRODUCTS

## (57) Abstract

The compounds of the present invention are of the formula (I):  $A-X-(CH_2)_n-Y-(CH_2)_m-Z$  wherein: A is a non-steroidal anti-inflammatory agent (NSAIA); A-X is an ester or amide linkage derived from the carboxylic acid moiety of the NSAIA, wherein X is O or NR; R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl; Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n</sub>; n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n</sub>; n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present; n is 1 to 4 and m is 0 to 4 when Y is CH(OH); n' is 0 to 2; and Z is (a), (b), (c), (d) or (e) wherein: R' and R<sup>3</sup> are H, C(O)R, C(O)N(R)<sub>2</sub>, PO<sub>3</sub><sup>-</sup>, or SO<sub>3</sub><sup>-</sup>; R'' is H or C<sub>1</sub>-C<sub>6</sub> alkyl; and R' and R<sup>3</sup> together may form a ring having structure: (1) or (2); and provided that when Z is (e), X is not O. The compounds of the present invention also include pharmaceutically acceptable salts of the compounds of formula (I). Methods for treating inflammatory pathologies are disclosed. Particularly, the methods utilize pharmaceutical compositions containing certain compounds having an anti-inflammatory and anti-oxidant moiety covalently linked by an amide or ester bond. The compounds are useful in preventing and treating inflammatory disorders through several mechanisms.



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**ESTERS AND AMIDES OF NON-STEROIDAL ANTI-INFLAMMATORY  
CARBOXYLIC ACIDS WHICH MAY BE USED AS ANTI-OXIDANTS,  
5-LIPOXYGENASE INHIBITORS AND NON-STEROIDAL  
ANTI-INFLAMMATORY PRODUCTS**

The present application is a continuation-in-part of United States Patent  
Application Serial No. 08/362,718, filed December 23, 1994 and United States Patent  
Application Serial No. 08/472,445, filed on June 7, 1995.

**Background of the Invention**

The present invention is directed to the provision of compounds having potent anti-inflammatory and anti-oxidant activity. The invention is further directed to compositions containing the compounds of the present invention for use in pharmaceutical applications.

The present invention is also directed to various methods of using the compounds and compositions of the present invention in pharmaceutical applications including: 1) the treatment of inflammatory disorders including ocular inflammation associated with ophthalmic disease and ophthalmic surgery; 2) the prevention of corneal haze following

ocular surgery; 3) tissue preservation including cornea preservation during transplantation procedures; and 4) as an adjunct to heart disease therapy.

Inflammation from cellular stress can cause excessive tissue damage. Numerous biochemical pathways are known to lead to inflammation. In general, the cyclooxygenase system produces prostaglandins, while the lipoxigenase system produces leukotrienes, "HETEs" and "HPETEs". Such agents have been associated with inflammation. See generally, Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 600-617, Pergman Press, NY (1990). Therapies designed to inhibit the production of these types of agents are therefore of great interest.

Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIA's:

Ophthalmoscope, volume 8, page 257 (1910);

Nature, volume 231, page 232 (1971);

EASEB Journal, volume 1, page 89 (1987); and

Inflammation and Mechanisms and Actions of Traditional Drugs, Vol. I

Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, FL, CRC Press, (1985).

However, there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects (Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

Free radical molecules also play a major role in inflammation. These unstable chemical moieties lead to the oxidation of tissue resulting in damage. Such oxidative stress and damage has been described in Biochemical Pharmacology, 32(14), 2283-2286 (1983) and Free Radicals in Biology and Medicine, 4, 225-261 (1988). Agents that act as anti-oxidants can protect against oxidative damage. Such protection has been the subject of numerous scientific publications, including the following:

Archives of Pharmacology, volume 325, pages 129-146 (1992);

Journal of Photochemistry and Photobiology, volume 8, pages 211-224 (1991);

Free Radicals in Biology and Medicine, volume 11, pages 215-232 (1991);

and

European Journal of Pharmacology, volume 210, pages 85-90 (1992).

The combination of anti-oxidant activity with other pharmacologically significant activities in a single molecule is discussed in JP 010484 A2 and EP 387771 A2; and compounds with cyclooxygenase/5-Lipoxygenase and anti-oxidant activity are discussed in Drug Research, 39(II) Number 10, pages 1242-1250 (1989). However, these references do not disclose the compounds of the present invention.

Ocular inflammation is a condition which generally affects the patient with scratchiness, itchiness and/or red eye. Ocular inflammation can be initiated by various insults. For example, ocular inflammation can result from allergic response to various allergens, trauma to the eye, dry eye and surgical complications. Various anti-inflammatory therapies are currently in use for the treatment of ocular inflammation including the topical administration of diclofenac.

Ocular surgery can result in various post-surgical complications to the eye. Such complications generally include: 1) loss of vascular blood barrier function; 2) tissue edema including conjunctiva swelling, conjunctiva congestion and corneal haze; 3) cataract formation; and 4) loss of membrane integrity including decrease in docosahexanoic acid levels in membrane phospholipids.

As stated above, vitrectomy surgery can induce a variety of post-surgical complications. Many of these complications are further potentiated in diabetic patients who are at risk for many ocular pathologies. Posterior segment surgery due to the severity of the surgical procedure can cause extensive tissue damage at both the acute and chronic phases of the recovery process. The acute phase of the postsurgical period is characterized by both ocular neovascularization and tissue edema. This is caused by breakdown of the blood aqueous and blood retinal barrier functions resulting in sustained vascular permeability following the surgical trauma. The presence of elevated inflammatory and serum factors induce cell proliferation during the normal wound healing process. Slitlamp clinical examinations at 24 hours have indicated extensive anterior chamber flare and cell influx, conjunctiva congestion and swelling (with discharge), iritis, and corneal haze. See for example, Kreiger, A.E., *Wound Complications In Pars Plana Vitrectomy*, Retina, volume 13, No. 4, pages 335-344 (1993); Cherfan, G.M., et al., *Nuclear Sclerotic Cataract After Vitrectomy for Idiopathic Epiretinal Membranes Causing Macular Pucker*, American Journal Of Ophthalmology, volume 111, pages 434-438 (1991); Thompson, J.T., et al., *Progression of Nuclear Sclerosis and Long-term Visual Results of Vitrectomy With Transforming Growth Factor Beta-2 for Macular Holes*, American Journal Of

Ophthalmology, volume 119, pages 48-54 (1995) and Dobbs, R.E., et al., *Evaluation Of Lens Changes In Idiopathic Epiretinal Membrane*, volume 5, Nos. 1 & 2, pages 143-148 (1988).

The chronic phase of the postsurgical period is characterized by more severe complications that can necessitate additional surgery. These include an incidence of recurrent retinal detachment, epiretinal proliferation, neovascular glaucoma, corneal problems, vitreous hemorrhage, rate of cystoid macular edema, and occurrence of cataract formation within six months of surgery.

The frequency of these complications can be lessened by facilitating the recovery of vascular leakage and limiting the duration of the cellular proliferative response by introduction of therapeutic compounds into the irrigating solution during the time of surgery.

Organ or tissue transplantation requires the preservation of the tissue from the time of excision from the donor to the time of transplantation into the recipient. During this time the tissue can become inflamed and even die. Methods of preserving the tissue have included the use of various temperature conditions, the use of chondroitin sulfate and the use of anti-inflammatory agents (Lindstrom, R.L., et al., *Corneal Preservation at 4°C with Chondroitin Sulfate-Containing Medium*, The Cornea: Transactions of the World Congress on the Cornea III, edited by H. Dwight Cavanagh, Raven Press, Ltd., New York, Chapter 14, pages 81-89 (1988); and Guo, A., et al., *Effects of anti-inflammatory and immunosuppressive drugs on the heterolamellar corneal transplantation in rabbits*, Current Eye Research, volume 9, No. 8, pages 749-757 (1990)).

Oxidation of various biomolecules in the vasculature has been implicated in numerous cardiovascular pathologies including atherosclerosis, thrombosis, myocardial infarction and congestive heart failure. In particular, several reports demonstrate a correlation between the oxidation of low-density lipoproteins (LDL) and the progression of atherosclerotic lesions (New England Journal of Medicine, volume 328(20), pages 1444-1449 (1993)). These oxidized LDLs have been further characterized in several pathological events including: 1) chemotaxis, which draws monocytes to the afflicted tissue; 2) differentiation of monocytes into macrophages; 3) uptake of LDL by macrophages to form foam cells; 4) proliferation of smooth muscle cells; 5) development of atherosclerotic lesions; and 6) cytotoxic effects on endothelial cells as well as increases in arterial vasoconstriction (JAMA, volume 264(3), pages 3047-3052 (1990)).

The use of antioxidants to ameliorate coronary heart disease has been explored. Epidemiological studies have correlated the dietary intake of Vitamin E with reduced risk to coronary heart disease (New England Journal of Medicine, volume 328(20), pages 1444-1449 (1993); and New England Journal of Medicine, volume 328(20), pages 1450-156 (1993)).  $\beta$ -carotene, a naturally occurring anti-oxidant, has been pursued in the clinic for cardiovascular disease indications (Scrip No., 1574:31 (1990)). Additionally, research has shown that treatment of hypercholesterolemic animals with antioxidant drugs, including the phenolic antioxidant compound, probucol, has reduced the development of atherosclerosis (Proceedings of the National Academy of Science, U.S.A., volume 84, pages 7725-7729 (1989)).



Oxygen radicals have also been implicated in the pathogenesis of a number of other inflammatory conditions. Such conditions have included stroke, rheumatoid arthritis, retinopathy and endotoxic liver injury. It is believed that anti-oxidants would be useful in treating such conditions (Methods in Enzymology, volume 186, pages 1-85 (1990)).

Anti-inflammatory therapy has been suggested as an adjuvant to the treatment of various cardiovascular indications. These agents assist in preventing thrombotic and atherosclerotic occlusions and restenosis of the vasculature by inhibiting platelet and leukocyte aggregation.

As such, aspirin has been prescribed broadly, for anti-inflammatory and analgetic indications, as well as for patients with unstable angina. Ibuprofen and naproxen have been prescribed for treatment of rheumatoid arthritis and moderate pain. However, there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects (Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

The present invention is directed to the provision of new compounds that have both potent anti-inflammatory activity and potent anti-oxidant activity in a single molecule. The use of a single chemical entity with potent anti-inflammatory and potent anti-oxidant activity provides increased protection relative to the use of a compound with singular activity. The use of a single agent having both activities over a combination of two different agents provides uniform delivery of an active molecule, thereby simplifying issues of drug metabolism, toxicity and delivery.

### Summary of Invention

The present invention provides methods of using novel compounds having potent anti-inflammatory and anti-oxidant activity for the treatment inflammatory conditions such as tissue edema, vascular permeability, ophthalmic itchiness scratchiness or irritation, and vascular diseases. The dual therapeutic efficacies may act in an additive or synergistic manner to reduce cellular damage. Additionally, the compounds of the present invention also exhibit other anti-inflammatory activity not present in the individual agents.

The compounds of the present invention are useful as cytoprotective agents due to their anti-oxidant activity. These compounds include both a non-steroidal anti-inflammatory agent (NSAIA) moiety and an anti-oxidant moiety. In order to provide effective therapy for inflammatory disorders, the present invention takes advantage of these individual efficacies. In addition, the present invention improves upon these individual efficacies by providing greater drug delivery to the target tissues by means of administering a single drug having multiple therapeutic actions. The present invention also provides compounds that associate with lipid membranes, thus providing bioavailable anti-oxidant protection within lipid molecules susceptible to oxidation. Finally, the compounds of the present invention exhibit therapeutic properties which are not present in the individual moieties of the compounds. These and other advantages of the present invention will be apparent to those skilled in the art based on the following description.

The NSAIA component of the compounds provides anti-inflammatory activity when it is freed from the parent compound. The use of these NSAIAs will provide inhibition of cyclooxygenase, an important enzyme involved in the prostaglandin/inflammation pathway. The compounds also include an anti-oxidant component. As oxidative stress has been implicated in inflammatory responses, the presence of an anti-oxidant will further help treat the target tissue.

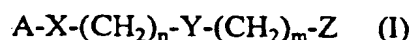
The compounds of the present invention also exhibit intrinsic properties present only in the combined molecule, not in the individual components. One such property is the inhibitory efficacy against 5-lipoxygenase, an enzyme known to be involved in inflammation.

Another advantage of the present invention is that the anti-inflammatory moiety and the anti-oxidant moiety are linked through an amide or ester bond. Since the carboxylic acid moiety of the NSAIA has been converted to an amide or ester, the resultant molecule is neutrally charged, thus increasing lipophilicity, and drug delivery. These compounds also associate with lipid membranes, thus providing resident antioxidant protection of these oxidizable biomolecules. Furthermore, amide or ester pro-drugs, may provide site-directed anti-inflammatory activity since amidases and esterases, components of the inflammatory response, will catalyze the hydrolysis of the amide or ester and release the non-steroidal anti-inflammatory agent and anti-oxidant.

The compounds of the present invention are capable of protecting against cellular damage by a wide range of insults. Since the compounds provide this protection by decreasing free radical or oxidative damage, reducing enzyme mediated inflammation, and improving site delivery, this therapy represents an improved two-pronged approach to the treatment of inflammatory pathologies.

#### Detailed Description of Invention

The compounds of the present invention are of the formula (I):



wherein:

A is a non-steroidal anti-inflammatory agent (NSAIA);

A-X is an ester or amide linkage derived from the carboxylic acid moiety of the NSAIA, wherein X is O or NR;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n</sub>;

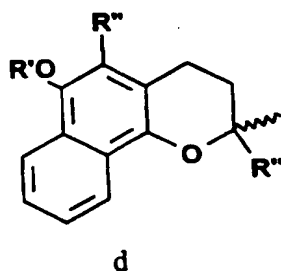
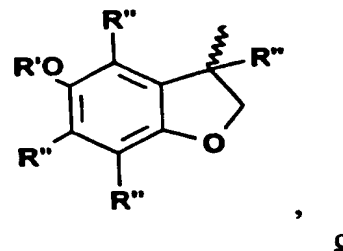
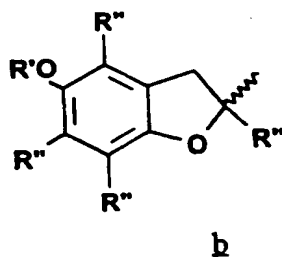
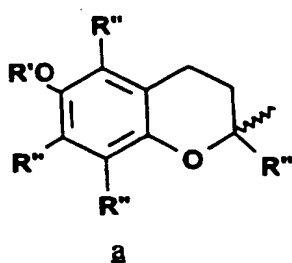
n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n</sub>;

n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present;

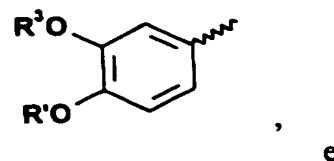
n is 1 to 4 and m is 0 to 4 when Y is CH(OH);

n' is 0 to 2; and

Z is:



or

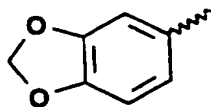


wherein:

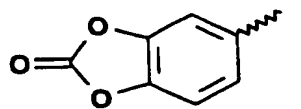
R' and R<sup>3</sup> are H, C(O)R, C(O)N(R)<sub>2</sub>, PO<sub>3</sub><sup>-</sup>, or SO<sub>3</sub><sup>-</sup>;

R'' is H or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R' and R<sup>3</sup> together may form a ring having the following structure:



or



and provided that when Z is e, X is not O.

The compounds of the present invention also include pharmaceutically acceptable salts of the compounds of formula (I).

The compounds of the present invention contain a non-steroidal anti-inflammatory agent, "A", having a carboxylic moiety. A number of chemical classes of non-steroidal anti-inflammatory agents have been identified. The following text, the entire contents of

which are hereby incorporated by reference in the present specification, may be referred to for various NSAIA chemical classes: CRC Handbook of Eicosanoids: Prostaglandins, and Related Lipids, Volume II. Drugs Acting Via the Eicosanoids, pages 59-133, CRC Press, Boca Raton, FL (1989). The NSAIA may be selected, therefore, from a variety of chemical classes including, but not limited to, fenamic acids, such as flufenamic acid, niflumic acid and mefenamic acid; indoles, such as indomethacin, sulindac and tolmetin; phenylalkanoic acids, such as suprofen, ketorolac, flurbiprofen and ibuprofen; and phenylacetic acids, such as diclofenac. Further examples of NSAIAs are listed below:

	tolfenamic acid	indoprofen
pirprofen	clidanac	fenoprofen
naproxen	fenclorac	meclofenamate
benoxaprofen	carprofen	isofezolac
aceloferac	fenbufen	etodolic acid
fleclozic acid	amfenac	efenamic acid
bromfenac	ketoprofen	fenclofenac
alcofenac	orpanoxin	zomopirac
diflunisal	pranoprofen	zaltoprofen

The preferred compounds are those wherein "A" is selected from the ester or amide derivatives of naproxen, flurbiprofen or diclofenac. The most preferred compounds are those wherein "A" is selected from the ester or amide derivatives of naproxen or flurbiprofen.

With respect to the other substituents of the compounds of formula (I), the preferred compounds are those wherein:

X is O or NR;

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), and m is 0 to 2 and n is 1 or 2, or Y is not present, and m is 1 or 2 and n is 0 to 4;

Z is a, b, d or e;

R' and R<sup>3</sup> are H or C(O)CH<sub>3</sub>; and

R'' is CH<sub>3</sub>.

The most preferred compounds are those wherein:

X is O or NR;

R is H;

Y is CH(OH) or is not present;

m is 0 or 1;

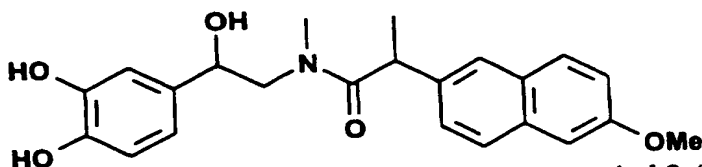
n is 1;

Z is a, b, d or e;

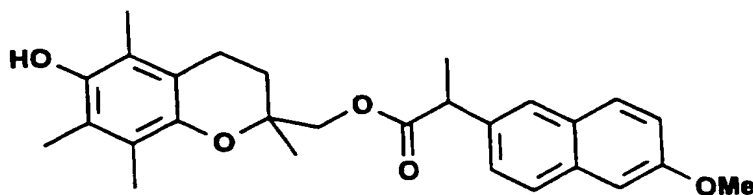
R' and R<sup>3</sup> are H; and

R'' is CH<sub>3</sub>.

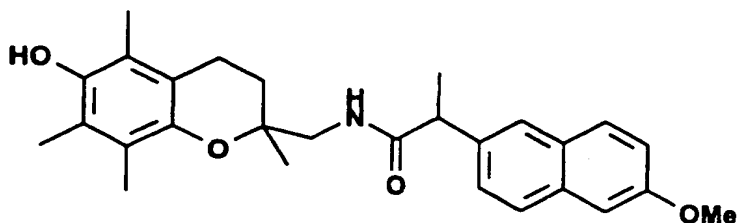
The following compounds are particularly preferred:



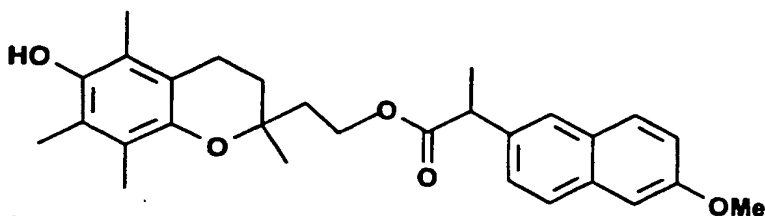
15 N-(2-(3,4-dihydroxyphenyl)-2-hydroxyethyl)-N-methyl 2-(6-methoxy-2-naphthyl)propionamide ("Compound A");



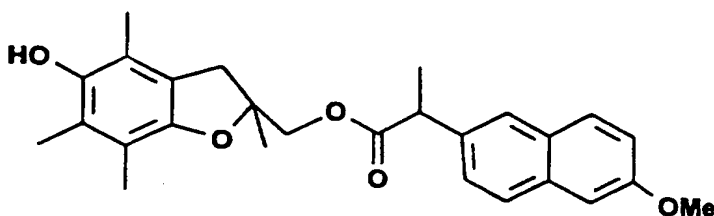
2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)methyl 2-(6-methoxy-2-naphthyl)propionate ("Compound B");



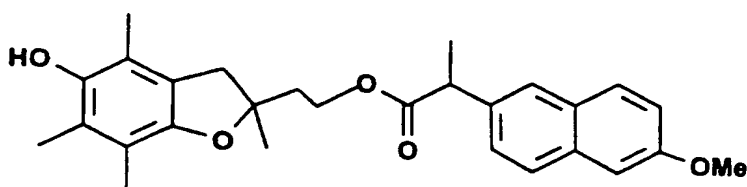
N-(2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)methyl) 2-(6-methoxy-2-naphthyl)propionamide ("Compound C");



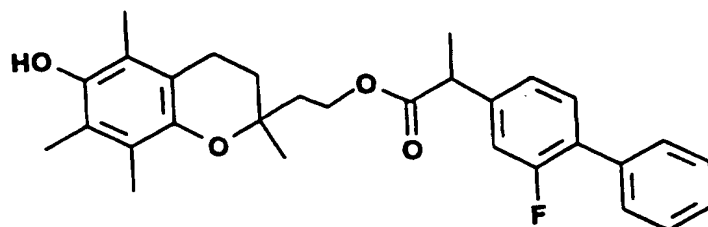
2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate ("Compound D");



2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-benzo[1,2-b]furan-2-yl)methyl 2-(6-methoxy-2-naphthyl)propionate ("Compound E");



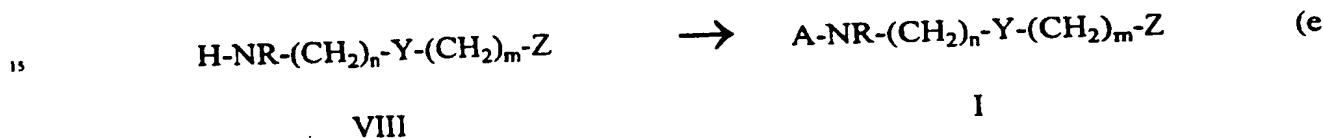
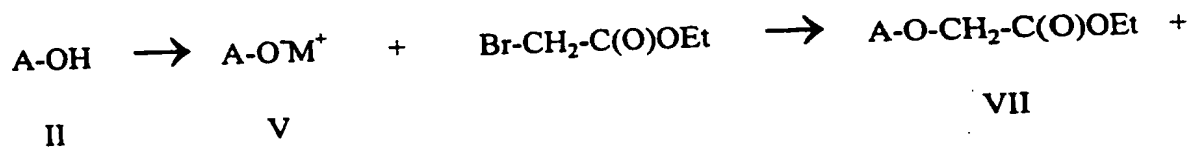
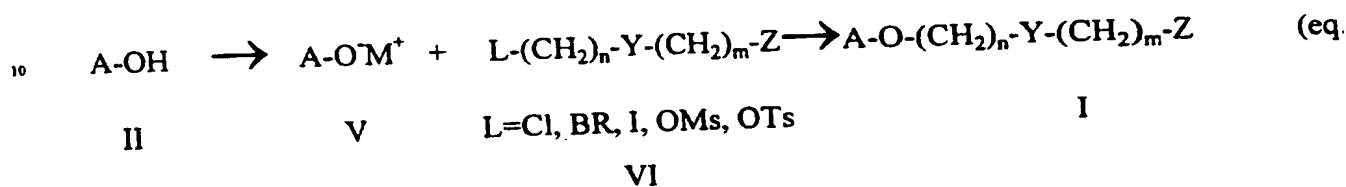
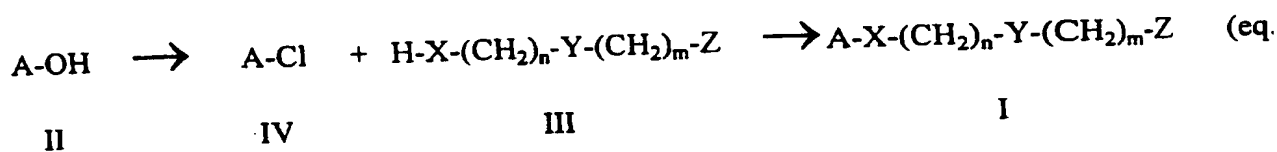
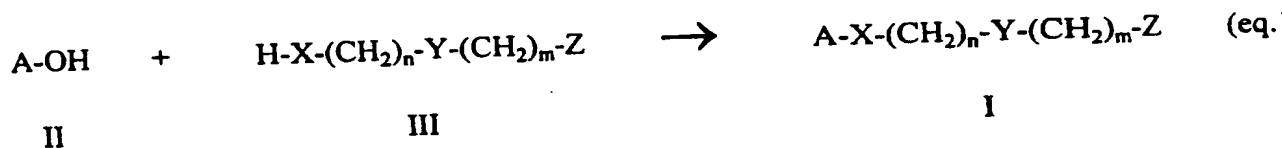
2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-benzo[1,2-b]furan-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate ("Compound F"); and



2-(6-hydroxy-2,5,7,8-tetramethyl-2,3-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate ("Compound G").

The compounds of the present invention may be prepared by the methods illustrated in Scheme 1 below:

Scheme 1





The conversion of the carboxylic acid containing nonsteroidal anti-inflammatory agents (II) to esters or amides (I) may be carried out by the following methods:

(i) As illustrated in equation 1 above, carboxylic acids (II) may be reacted with the appropriate amine or alcohol derivative (III) in the presence of a coupling reagent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl, and 4-dimethylamine pyridine or 1-hydroxybenzotriazole, in an inert organic solvent, such as acetonitrile or tetrahydrofuran, and at a temperature from 0°C to 50°C.

(ii) As illustrated in equation 2 above, carboxylic acids (II) may be converted to acid chlorides (IV) by reacting them with a reagent such as thionyl chloride or oxalyl chloride, in the presence of an inert solid or neat, at a temperature from 0°C to 80°C. The resulting acid chloride (IV) may be reacted with the desired amine or alcohol (III) in an inert solvent such as tetrahydrofuran, in the presence of pyridine or a tertiary amine, such as triethylamine.

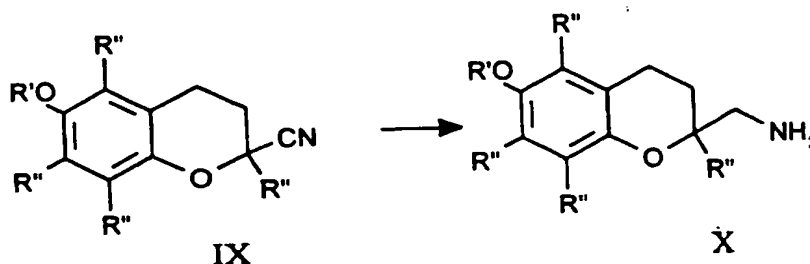
(iii) As illustrated in equation 3 above, esters (I) may be formed by reacting carboxylate anions (V), formed by reacting the carboxylic acid (II) with a base such as sodium hydride, with a halide (iodide, bromide, chloride) or sulfonate (mesylate, tosylate) (VI), in a solvent such as acetonitrile or dimethylformamide, at a temperature from 0°C to 100°C.

(iv) As illustrated in equation 4 above, amides (I) may be prepared by reacting carboxylate anions (V), formed by reacting carboxylic acid (II) with a base such as sodium hydride, with ethyl bromoacetate. The resulting ester (VII) is reacted with the desired amine (VIII), neat or in an inert solvent, such as acetonitrile or dimethylformamide, at a temperature from 0°C to 100°C.

The intermediate compounds (X) of Scheme 2 below, which can be used as compounds (III) and (VIII), were prepared using the general methods described in Journal of Organic Chemistry, volume 54, pages 3282-3292, (1989). The nitrile (IX) can be reduced using a reagent such as lithium aluminum hydride to afford the amine (X), which may be isolated as the hydrochloride salt.

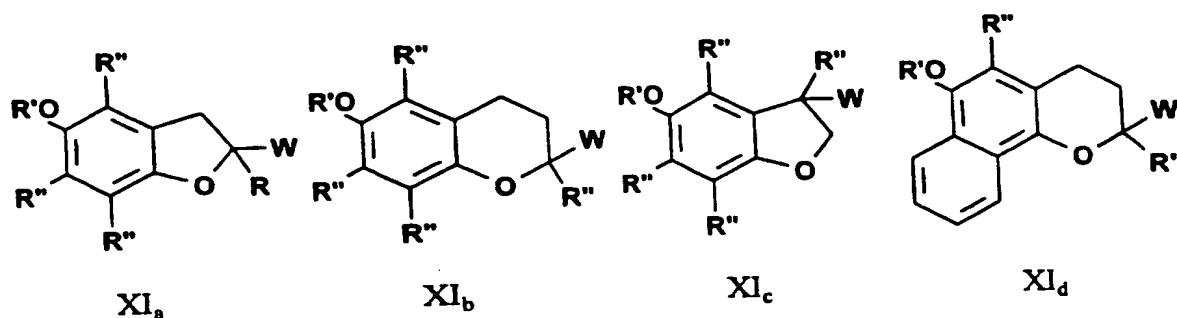
The use of certain protecting groups and deprotection steps may be necessary, as will be appreciated by those skilled in the art.

Scheme 2



Compounds of formula (I) may exist as mixtures of stereoisomers. The preparation of the individual stereoisomers may be effected by preparing and resolving the acids (II), by known methods, and then using a single stereoisomer as starting material. Compounds (III), (VI) and (VIII) may be prepared as single stereoisomers from compounds of formula (XI<sub>a-d</sub>), shown in Table 1 below, using known methods:

Table 1



wherein:

W is (CH<sub>2</sub>)<sub>p</sub>-Q;

p is 0-1;

Q is CH<sub>2</sub>OH or CO<sub>2</sub>H;

R' is H, C(O)R, C(O)NR<sub>2</sub>, PO<sub>3</sub><sup>-</sup>, or SO<sub>3</sub><sup>-</sup>; and

R" is H or C<sub>1</sub>-C<sub>6</sub> alkyl.

The alcohols (XI<sub>a-d</sub>) may be resolved by forming esters with optically active carboxylic acids, separating the diastereomers, and then hydrolyzing the resolved diastereomers. The corresponding carboxylic acids (XI<sub>a-d</sub>) may be resolved by forming an ester with an optically active alcohol, separating the diastereomers, and then hydrolyzing the resolved diastereomers. Or, the carboxylic acids (XI<sub>a-d</sub>) may be resolved by forming an amine salt with an optically active amine. Separation by recrystallization and neutralization of the resolved carboxylic acid salt may be utilized to provide the resolved carboxylic acid. Resolution of the esters and amides (I) may also be effected using chromatographic techniques known to those skilled in the art.

The amines of formula (I), where Y is NR, may be converted to amine salts by reacting the amine with acids of sufficient strength to produce an organic or inorganic salt.

The pharmaceutically acceptable anions include: acetate, bromide, chloride, citrate, maleate, fumarate, mesylate, phosphate, sulfate and tartrate.

Methods of synthesizing the compounds formula (I) are further illustrated by the following examples:

### Example 1

#### Synthesis of N-(2(3,4-dihydroxyphenyl)-2-hydroxyethyl)-N-methyl 2-(6-methoxy-2-naphthyl)propionamide

Epinephrine (Aldrich, 3.18 grams [g], 17.3 millimoles [mmol]), 1-hydroxylbenzotriazole hydrate (Aldrich, 1.76 g, 12.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl (Aldrich, 2.49 g, 12.9 mmol) were added to acetonitrile (200 milliliters [ml]). After stirring for 10 minutes, a solution of 6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid (Aldrich, 2.0 g, 8.66 mmol), in 50 ml of acetonitrile, was added dropwise. After stirring for 16 hours, the reaction mixture was concentrated in vacuo (under reduced pressure), and the residue was partitioned between water (100 ml) and methylene chloride (100 ml). The

layers were separated and the aqueous layer was extracted with methylene chloride (2 x 50 ml) and ethyl acetate (50 ml). The combined organic extracts were treated with methanol until a clear solution was formed. This solution was dried (magnesium sulfate) and concentrated in vacuo. Flash chromatography of the residue (silica gel, 95:5, volume:volume [v:v], methylene chloride:methanol), and concentration of the appropriate fractions resulted in the formation of a solid. The solid was recrystallized from a mixture of ethyl acetate and hexane to give N-(2(3,4-dihydroxyphenyl)-2-hydroxyethyl)-N-methyl-2-(6-methoxy-2-naphthyl)propionamide, a mixture of diastereomers, as a white solid (0.95 g, 27% yield).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25-1.49 (m, 3H), 2.88 (d, 3H), 3.75-4.20 (m, 2H), 3.90 (s, 3H), 4.80 (m, 1H), 6.5-7.8 (m, 12H).

Elemental Analysis: Calculated for C<sub>23</sub>H<sub>25</sub>NO<sub>5</sub> · 0.5 H<sub>2</sub>O

Calculated for: C, 68.30; H, 6.48; N, 3.46.

Found: C, 68.35; H, 6.49; N, 3.43.

Melting point: 115-117°C.

### Example 2

#### Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)methyl 2-(6-methoxy-2-naphthyl)propionate

A solution of 6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzo[1,2-b]pyran-2-yl)methanol (2.00 g, 8.46 mmol), 6-methoxy-α-methyl naphthaleneacetic acid (2.14 g, 9.31 mmol), 20 dimethylaminopyridine (Aldrich, 1.24 g, 10.00 mmol) and 1-(3-dimethylamino propyl)-3-ethyl-carbodiimide hydrochloride (1.71 g, 8.89 mmol), in tetrahydrofuran (40 mL), was stirred at ambient temperature under nitrogen for 72 hours. The reaction mixture was then diluted with ethyl acetate (200 mL), washed with 0.5 N hydrochloride (2x 250 mL), followed by water (2x 250 mL), and then dried (sodium sulfate) and concentrated in vacuo. Flash chromatography of the residue (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate), and concentration of the appropriate fractions provided an oil. Crystallization 25 from ethyl acetate-hexanes gave 2.21 g (58.3% yield) of an impure white solid. The solid

was then chromatographed, and the appropriate fractions were collected and concentrated. The solid that formed was recrystallized from a mixture of ethyl acetate and hexanes to give 0.80 g (21.1% yield) of a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15 (s, 3H), 1.57-1.61 (d, 3H), 1.62-1.88 (m, 2H), 1.98-2.11 (m, 9H), 2.40-2.59 (m, 2H), 3.82-3.92 (m, 1H), 3.91 (s, 3H), 4.01-4.22 (m, 3H), 7.09-7.16 (m, 2H), 7.34-7.41 (m, 1H), 7.55-7.68 (m, 2H).

Elemental Analysis: Calculated for C<sub>28</sub>H<sub>32</sub>O<sub>5</sub>.

Calculated: C, 74.98; H, 7.19.

Found: C, 75.15, H, 7.08.

Melting point: 103-105°C.

### Example 3

#### Synthesis of N-[(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methyl] 2-(6-methoxy-2-naphthyl)propionamide

The intermediate, (6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methylamine, was first synthesized:

A 1 molar (M) ethereal solution of lithium aluminum hydride (Aldrich, 32.4 mL, 32.43 mmol) was added slowly over a 5 minute period to a chilled, (4-6°C) stirring solution of (2-cyano-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran in tetrahydrofuran (50 mL). After 2 hours, the reaction mixture was quenched by the slow sequential addition of 10% aqueous tetrahydrofuran (30 mL), 15% sodium hydroxide (10 mL) and then water (20 mL), while stirring. The resulting suspension was filtered through celite, and the celite pad was washed with ethyl ether (400 mL). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo, resulting in a residue. A 1 M ethereal solution of hydrochloride was then added to a solution of the residue in ethyl ether (100 mL), a solid formed, and the solid was then collected by filtration and washed with ethyl ether to give 2.31 g (65.4% yield) of a white solid. The product was used crude in the next reaction.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>/TMS): 1.15 (s, 3H), 1.75 (t, 2H), 1.99 (s, 6H), 2.01 (s, 3H), 2.54 (t, 2H), 2.98 (s, 2H).

MS (CI): 236 (m+1).

The hydrochloride salt of (6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methylamine (0.30 g, 1.10 mmole) and 6-methoxy- $\alpha$ -methyl naphthaleneacetic acid (Aldrich, 0.28 g, 1.21 mmole) were stirred in the presence of dimethylaminopyridine (Aldrich, 0.26 g, 2.20 mmole) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Janssen Chimica-Spectrum, 0.21 g, 1.10 mmole), in tetrahydrofuran (4.0 mL) under an atmosphere of nitrogen. After stirring 17 hours at ambient temperature, the reaction mixture was diluted with ethyl acetate (70 mL), washed with water (2x 15 mL), followed by brine (15 mL) and then dried (sodium sulfate). The mixture was concentrated in vacuo and the residue subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate). The appropriate fractions were concentrated in vacuo, and the resulting crystalline foam suspension was then washed in hexanes to give 0.28 g (58.3% yield) of N-[(5-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-2-(6-methoxy-2-naphthyl)propionamide as a white amorphous solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  1.03-1.08 (d, 3H), 1.57-1.64 (m, 6H), 1.70 (t, 2H), 2.04-2.05 (m, 6H), 2.48-2.51 (m, 2H), 3.16-3.58 (m, 2H), 3.74 (q, 1H), 3.91 (s, 3H), 4.91 (br s, 1H), 5.751 (t, 1H), 7.01-7.19 (m, 2H), 7.29-7.40 (t, 1H), 7.52-7.81 (m, 3H).

Elemental Analysis: Calculated for C<sub>28</sub>H<sub>33</sub>NO<sub>4</sub>

Calculated: C, 75.14; H, 7.43; N, 3.13.

Found: C, 75.04; H, 7.50; N, 2.97.

Melting point: 67-70°C.

### Example 4

#### Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(6-methoxy-2-naphthyl)propionate

A solution of 1,3-dicyclohexylcarbodiimide (Aldrich, 0.89 g, 4.31 mmol) in acetonitrile (25 mL), was added dropwise to a stirring slurry of (+)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid (Aldrich, 0.90 g, 3.91 mmol), 2-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethanol (0.98 g, 3.91 mmol, USP 5,266,709 column 45) and 1-hydroxybenzotriazole hydrate (Aldrich, 0.59 g, 4.31 mmol), in acetonitrile (50 mL). After stirring for 18 hours, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between water (30 mL) and methylene chloride (30 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic extracts were washed with water (20 mL), then dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (silica gel, 2:8, v:v, ethyl acetate:hexanes) of the residue afforded a white solid upon the concentration of the appropriate fractions. The white solid was recrystallized from an ethyl acetate-hexanes mixture to give 0.60 g (33.1% yield) of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(6-methoxy-2-naphthyl)propionate, a mixture of diastereomers, as a white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.1 (d, 3H), 1.6-1.5 (m, 3H), 1.6 (m, 2H), 1.9 (m, 2H), 2.0 (s, 6H), 2.1 (s, 3H), 2.4 (t, 2H), 3.8 (q, 2H), 3.9 (s, 3H), 4.2 (s, 1H), 4.1-4.4 (m, 2H), 7.1-7.7 (m, 6H).

Elemental Analysis: Calculated for  $\text{C}_{29}\text{H}_{34}\text{O}_5$

Calculated: C, 75.30; H, 7.41.

Found: C, 75.24; H, 7.46.

Melting Point: 99.5-101.5°C.

**Example 5****Synthesis of 2-(5-hydroxy-2,4,6,7-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]furan-2-yl)-methyl 2-(6-methoxy-2-naphthyl)propionate**

A solution of (5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzo[1,2-b]furan-2-yl)-methanol (0.78 g, 3.50 mmol) and 6-methoxy- $\alpha$ -methyl naphthaleneacetic acid (Aldrich, 0.89 g, 3.86 mmol) was stirred in the presence of dimethylaminopyridine (0.43 g, 3.51 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.67 g, 3.51 mmol), in tetrahydrofuran (15 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 24 hours, diluted with water (100 mL) and then washed with ethyl acetate (5x 65 mL). The organic extracts were combined, and then dried (sodium sulfate) and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate), and the appropriate fractions were combined to give 0.68 g (44.7% yield) of a foam residue. Crystallization from methylene chloride-hexanes gave 0.24 g (15.8% yield) of a pale yellow solid.

<sup>1</sup>H-NMR CDCl<sub>3</sub>: 1.33-1.35 (d, 3H), 1.51-1.55 (d, 3H), 1.92-1.94 (s, 3H), 2.00-2.03 (d, 3H), 2.09-2.11 (d, 3H), 2.56-2.57 (d, 1H), 2.58-2.91 (d, 1H), 3.76-3.89 (m, 1H), 3.920 (s, 3H), 4.04-4.22 (m, 3H), 7.09-7.17 (m, 2H), 7.26-7.34 (m, 1H), 7.58-7.79 (m, 2H).

Elemental Analysis: Calculated for C<sub>27</sub>H<sub>30</sub>O<sub>5</sub>.

Calculated: C, 74.63; H, 6.96.

Found: C, 74.42; H, 6.94.

Melting point: 185.5-187°C.

**Example 6****Synthesis of 2-(5-hydroxy-2,4,6,7-tetramethyl-3,4-dihydro-benzo[1,2-b]furan-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate**

A solution of 2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzo[1,2-b]furan-2-yl)ethanol (1.30 g, 5.51 mmol) and 6-methoxy- $\alpha$ -methyl naphthaleneacetic acid (Aldrich, 1.39 g, 6.06



mmol) was stirred in the presence of dimethylaminopyridine (0.67 g, 5.51 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.06 g, 5.51 mmol), in tetrahydrofuran (25 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 24 hours, diluted with ethyl acetate (150 mL), washed with water (2x 40 mL) and then brine (30 mL). The organic extract was dried (sodium sulfate) and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate), and the appropriate fractions were combined to give 1.84 g (74.5% yield) of a foam residue. Fractional crystallization and recrystallization from methylene chloride-hexanes gave 0.40 g (13.0% yield) of white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.34 (s, 3H), 1.54-1.57 (d, 3), 1.99 (t, 2H), 2.01 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3), 2.73-2.81 (d, 1), 2.90-2.97 (d, 1), 3.77-3.89 (q, 1H), 3.91 (s, 3H), 4.102 (s, 1H), 4.165-4.29 (m, 2H), 7.10-7.16 (m, 2H), 7.35-7.40 (m, 1H), 7.64-7.70 (m, 2H).

Elemental Analysis: Calculated for C<sub>28</sub>H<sub>32</sub>O<sub>5</sub> · 0.1 mole CH<sub>2</sub>Cl<sub>2</sub>.

Calculated: C, 73.84; H, 7.10.

Found: C, 73.85, 73.83; H, 7.12.

Melting point: 129.5-131°C.

### Example 7

Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo [1,2-b]pyran-2yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate

The intermediate, 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate, was first synthesized:

A solution of flubiprofen (Sigma, 2.0 g, 8.2 mmol), 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethanol (2.4 g, 8.2 mmol) 1-hydroxybenzotriazole hydrate (Aldrich, 2.4 g, 13.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (Aldrich, 2.8 g, 12.3 mmol), in acetonitrile (40 ml), was stirred at ambient temperature. After 72 hours, the reaction mixture was concentrated in vacuo and the

residue partitioned between water and methylene chloride. A solid formed which was removed by filtration and discarded. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 25 ml). The combined organic extracts were then dried (magnesium sulfate) and concentrated in vacuo. The residue was chromatographed (silica gel, 2:8, v:v, ethyl acetate:hexane). Concentration of the appropriate fractions afforded 3.0 g (64% yield, mixture of stereoisomers) of the product as a clear oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.23-1.27 (m, 3H), 1.53-1.57 (m, 3H), 1.75 (m, 2H), 1.95 (m, 2H), 2.08 (s, 3H), 2.14 (s, 3H), 2.21 (s, 3H), 2.55 (t, 3H), 3.75 (m, 2H), 4.3 (m, 1H), 4.65 (s, 2H), 7.1-7.7 (m, 13H).

A solution of 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo [1,2-b]pyran-2-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate in ethyl acetate was treated with 10% palladium on charcoal (Aldrich, 0.5 g). The resulting mixture was hydrogenated on a Parr Apparatus [initial pressure 60 pounds/inch<sup>2</sup> (psi)]. After 18 hours, the reaction mixture was filtered, and the resulting solution concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 2:8, v:v, ethyl acetate:hexane). Concentration of the appropriate fractions afforded a clear oil. Hexane was added to the oil and a white solid formed upon standing. The white solid was collected by filtration to afford 0.91 g (36% yield) of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate as a mixture of stereoisomers.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.22-1.23 (m, 3H), 1.51-1.55 (m, 3H), 1.65-1.8 (m, 2H), 1.85-2.00 (m, 2H), 2.08 (s, 6H), 2.14 (s, 3H), 2.57 (t, 2H), 3.75 (q, 1H), 4.1-4.5 (m, 2H), 7.10-7.65 (m, 8H).

Elemental Analysis: Calculated for C<sub>30</sub>H<sub>33</sub>FO<sub>4</sub>.

Calculated: C, 75.60; H, 6.98.

Found: C, 75.69; H, 7.01.

Melting point: 85-87°C.

The compounds of formula (I) may be contained in various types of pharmaceutical compositions, in accordance with formulation techniques known to those skilled in the art. For example, the compounds may be included in tablets, capsules, solutions, creams, suspensions and other dosage forms adapted for oral administration; solutions and suspensions adapted for topical or parenteral use; and suppositories for rectal use.

The present invention is particularly directed to the provision of compositions adapted for treatment of inflammatory conditions. The compositions of the present invention will include one or more compounds of formula (I) and a pharmaceutically acceptable vehicle for said compound(s). Various types of vehicles may be utilized. Suspensions may be preferred for compounds of formula (I) which are relatively insoluble in water.

An appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

Some of the compounds of formula (I) may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: polyethoxylated castor oils, Polysorbate 20, 60 and 80; Pluronic® F-68, F-84 and P-103 (BASF Corp., Parsippany NJ, USA); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01 to 2 wt.%.  
20

The pharmaceutical compositions containing one or more compound of formula (I) may be used to treat patients afflicted with or prone to various types of cellular damage. In particular, these compositions may be used for inflammation where prostaglandins, leukotrienes and cytokines are known to participate. The concentrations of the compounds in the compositions will depend on various factors, including the nature of the condition to be treated with the compositions. However, the compositions may contain one or more of the compounds of the present invention in a concentration of from about 0.001 to about 5 wt.%, for topical administration.

The route of administration (e.g., topical, parenteral or oral) and the dosage regimen will be determined by skilled clinicians, based on factors such as the exact nature  
30

of the condition being treated, the severity of the condition, the age and general physical condition of the patient, and so on.

As indicated above, compounds of formula (I) may be used to treat ocular inflammation at the cellular level and represents a particularly important aspect of the invention. The compounds are also useful in treating post-surgical complication resulting from ocular surgery. Treatment of the patient pre- or post-surgery with compounds of formula (I) may alleviate such conditions as tissue edema, neovascularization, conjunctiva swelling and congestion, corneal haze and cataract formation.

As indicated above, compound of formula (I) may also be used to preserve organs or tissue during the interim period between excision and transplantation. The compound are particularly useful in preserving corneas for transplantation.

As indicated above, compounds of formula (I) may also be used to prevent or reduce damage to vascular tissues at the cellular level. As used herein, "vascular inflammatory pathologies" refers to inflammation of the vasculature resulting from oxidation-mediated stress or stress mediated by other biochemical agents, such as cyclooxygenase or lipoxygenase inflammatory products. Vascular inflammatory pathologies which may be treated include, but are not limited to, atherosclerosis, thrombosis, hypercholesterolemia, congestive heart disease, stroke and unstable angina. The compounds may also be used as an adjunct to cardiac or brain surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be used prophylactically to treat high-risk heart disease patients.

The compounds and compositions of the present invention will be used in a therapeutically effective amount. As used herein, a "therapeutically effective amount" is that amount required to prevent, reduce or ameliorate cellular inflammation. The doses utilized for any of the above-described purposes will generally be from about 0.01 to about 100 milligrams per kilogram of body weight (mg/kg). When topically administered they will be dosed one to four times per day.

The compounds of the present invention are further illustrated by the following in vitro and in vivo biological activity examples.

### **Example 8**

The antioxidant activity of representative compounds of the present invention, as compared with Vitamin E, is presented in Table 2 below. Antioxidant activity was measured using a phospholipid oxidation assay. Liposomes were formed from dilinoleoylglycerolphosphatidylcholine and the test compound. Free radical damage was induced by exposure to  $\text{Fe}^{+3}$ /EDTA (167 micromolar [ $\mu\text{M}$ ]) and ascorbate (167  $\mu\text{M}$ ). Oxidation was terminated after one hour by freezing in liquid nitrogen. Lyophilized samples were then dissolved in methanol or water. Oxidation was measured by conjugate diene formation, monitored using UV spectroscopy as described in Biochimica et Biophysica Acta, volume 1081, 181-187, (1991). The  $\text{IC}_{50}$  was calculated using the following non-linear regression algorithm:  $Y = A/[1+(B/X)^c]$ , wherein A = maximum, B =  $\text{IC}_{50}$  and c = cooperativity or relative broadness of the curves. The minimum was assumed to be zero.

**Table 2**

Compound	Phospholipid Oxidation $\text{IC}_{50}$ ( $\mu\text{M}$ )
Compound B	1.16
Compound D	2.23
Compound E	2.48
Compound F	2.55
Vitamin E	4.42

**Example 9**

Inhibition of lipid peroxide formation by representative compounds of the present invention, as compared with Vitamin E, is shown in Table 3 below. The cytoprotective effects of the compounds were measured using bovine retinal pieces. Retinal tissues were incubated in hypoxic media for 1 hour. After 50 minutes of hypoxia, test agents were added to the media to allow 10 minutes for the drug to diffuse into the tissue prior to reoxygenation. The vehicle by itself, was added to the non-drug group. Following the incubation period, tissue was reoxygenated for 1 hour. Lipid peroxidation was assessed by the formation of thiobarbituric acid reacting substances (TBARS). The tissues were homogenized and added to the trichloroacetic acid-thiobarbituric acid reagent and heated in the presence of BHT. The homogenate was filtered and the absorbance of the supernatant was measured spectrophotometrically. A double derivative technique was used to calculate the concentration of TBARS present in each sample. Quantitation was based on a molar extinction coefficient of  $1.56 \times 10^5$ .

**Table 3**

Compound	Retinal Pieces IC <sub>50</sub> (μM)
Compound A	0.15
Compound D	0.006
Compound E	0.01
Vitamin E	5.0

**Example 10**

5-lipoxygenase inhibition by representative compounds of the present invention is shown in Table 4 below. The 5-lipoxygenase inhibitor activity was determined by measuring the inhibition of 5-HETE and LTB<sub>4</sub> formation. The ability of a compound to suppress 5-HETE and LTB<sub>4</sub> formation was investigated in calcium ionophore (A<sub>23187</sub>)-

stimulated neutrophils isolated from rabbit peripheral blood. Neutrophils were isolated by standard procedures. Briefly, heparinized/calcium chelated blood was obtained from New Zealand Albino (NZA) rabbits by heart puncture. Red cells were removed at 4°C by dextran sedimentation, as described in Blood, volume 11, 436 (1956). White cells, contained in the supernatant fraction, were sedimented by centrifugation and contaminating red cells removed by hypotonic lysis. The white cell pellet obtained, following red cell lysis and centrifugation, was resuspended in Dulbecco's PBS (Ca<sup>2+</sup>/Mg<sup>2+</sup>-free) and layered onto a 60% Histopaque-1083®/40% Histopaque-1119® cushion (Sigma Chemical, St. Louis, Missouri, U.S.A.). The Histopaque® cushion was then centrifuged, and the resulting neutrophil pellet was washed and resuspended in 1/25 of the original blood volume. Aliquots of the cell suspension were pretreated for 5 minutes at 37°C with carrier (DMSO) or test article dissolved in DMSO. CaCl<sub>2</sub> was immediately added to the cell suspension and cells stimulated by addition of 5 microliters [μl] of a mixture containing [1-<sup>14</sup>C]-arachidonic acid and A<sub>23187</sub> in DMSO. Final concentrations of CaCl<sub>2</sub>, [1-<sup>14</sup>C]-arachidonic acid and A<sub>23187</sub> were 5.0 millimolar [mM], 52 μM and 5.0 μM, respectively. After 3 minutes of incubation at 37°C, reactions were terminated by addition of 2 volumes of acetone. Extraction and reversed phase (C<sub>18</sub>-5μ) HPLC analysis of [1-<sup>14</sup>C]-labeled arachidonic acid metabolites are conducted as described by Graff and Anderson in Prostaglandins, volume 38, 473 (1989).

**Table 4**

Compound	5-Lipoxygenase Inhibition IC <sub>50</sub> (μM)
Compound A	4.0
Compound D	1.0

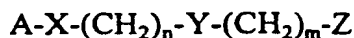
**Example 11**

A representative compound of the present invention, Compound D, was evaluated for its ability to interact with phospholipids in monolayers and bilayers. The procedures employed to evaluate lipid interaction with lipophilic agents have been described elsewhere (Biochemistry, volume 34, pages 7271-7281 (1995), and Langmuir, volume 8, pages 563-570 (1992)). From these studies, it was apparent that Compound D exhibits minimal intrinsic surface-active properties. In spite of its low endogenous surface-activity, Compound D partitioned from the aqueous solution into the phospholipid monolayer at initial packing densities exceeding those believed to exist in membranes. This finding supports an energetically favorable interaction between phospholipids and representative compounds of the present invention (e.g., Compound D). Assessment of Compound D's interaction with phospholipids in a liquid-expanded monolayer state also indicated eutectic-type phase diagrams with a solubility approaching 20 to 30 mole percent in dipalmitoylphosphatidylcholine. Additional evidence for its ability to interact with phospholipids was obtained by an alteration in the fluorescence of pyrene-labeled phospholipid in a liquid-crystalline phospholipid bilayer.



What is claimed is:

## 1. A compound of formula:



wherein:

A is a non-steroidal anti-inflammatory agent having a carboxylic moiety;

X is O or NR;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n'</sub>;

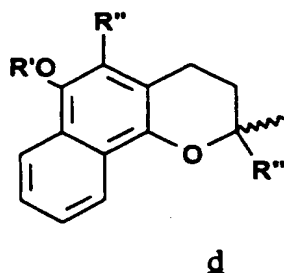
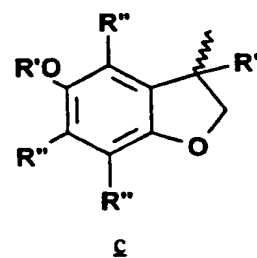
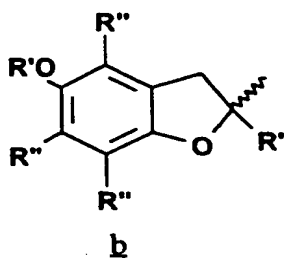
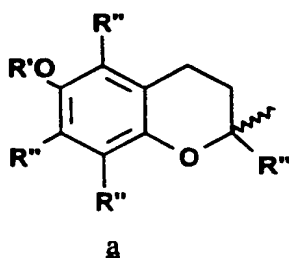
n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n'</sub>;

n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present;

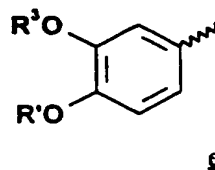
n is 1 to 4 and m is 0 to 4 when Y is CH(OH);

n' is 0 to 2; and

Z is selected from the group consisting of:



, and

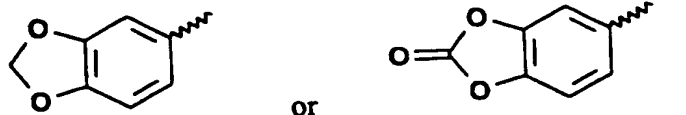


wherein:

R' and R<sup>3</sup> are H, C(O)R, C(O)N(R)<sub>2</sub>, PO<sub>3</sub><sup>-</sup> or SO<sub>3</sub><sup>-</sup>;

R" is H or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R' and R<sup>3</sup> together may form a ring having the following formula:



provided that when Z is e, X is not O, or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein:

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), m is 0 to 2, and n is 1 or 2, or Y is not present, m is 1 or 2, and n is 0 to 4;

Z is a, b, d or e;

R' and R<sup>3</sup> are H, C(O)CH<sub>3</sub>; and

R" is CH<sub>3</sub>.

3. The compound according to Claim 1, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: fenamic acids; indoles; phenylalkanoic acids; and phenylacetic acids.

4. The compound according to Claim 3, wherein:

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), m is 0 to 2, and n is 1 or 2, or Y is not present, m is 1 or 2, and n is 0 to 4;

Z is a, b, d or e;

R' and R<sup>3</sup> are H, C(O)CH<sub>3</sub>; and

R" is CH<sub>3</sub>.

5. The compound according to Claim 1, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of:

loxoprofen; tolfenamic acid; indoprofen; piroprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; acecloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; bromfenac; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen; ibuprofen; and diclofenac.

6. The compound according to Claim 5, wherein:

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), m is 0 to 2, and n is 1 or 2, or Y is not present, m is 1 or 2, and n is 0 to 4;

Z is a, b, d or e;

R' and R<sup>3</sup> are H, C(O)CH<sub>3</sub>; and

R" is CH<sub>3</sub>.

7. The compound according to Claim 1, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of naproxen, flurbiprofen and diclofenac.

8. The compound according to Claim 7, wherein A is naproxen.

9. The compound according to Claim 7, wherein A is flurbiprofen.

10. The compound according to Claim 7, wherein A is diclofenac.

11. The compound according to Claim 7, wherein:

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), wherein m is 0 to 2 and n is 1 or 2, or Y is not present, wherein m is 1 or 2 and n is 0 to 4;

Z is a, b, d or e;

R' and R<sup>3</sup> are H, C(O)CH<sub>3</sub>; and

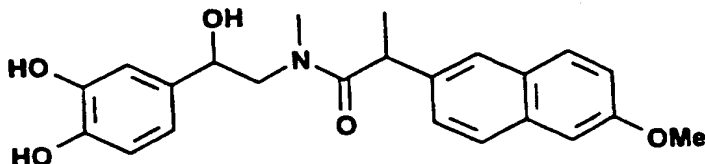
R'' is CH<sub>3</sub>.

12. The compound according to Claim 11, wherein A is naproxen.

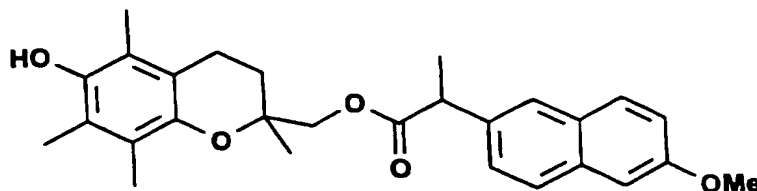
13. The compound according to Claim 11, wherein A is flurbiprofen.

10 14. The compound according to Claim 11, wherein A is diclofenac.

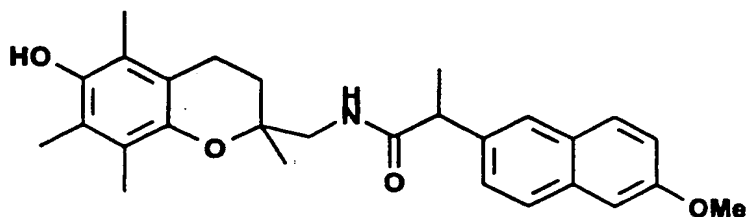
15. The compound according to Claim 1, wherein the compound has the following formula:



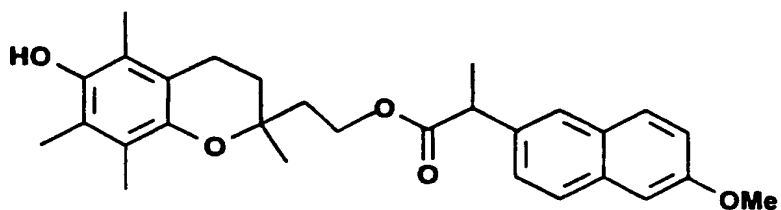
15 16. The compound according to Claim 1, wherein the compound has the following formula:



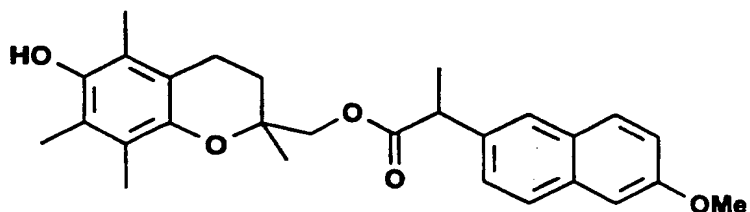
17. The compound according to Claim 1, wherein the compound has the following formula:



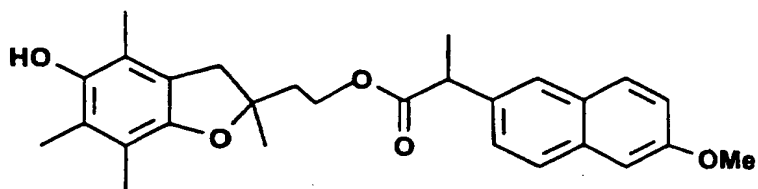
18. The compound according to Claim 1, wherein the compound has the following formula:



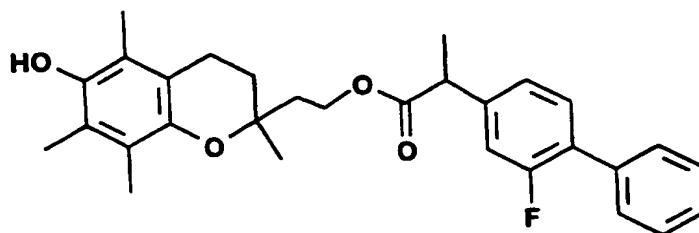
19. The compound according to Claim 1, wherein the compound has the following formula:



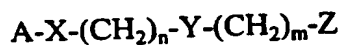
20. The compound according to Claim 1, wherein the compound has the following formula:



21. The compound according to Claim 1, wherein the compound has the following formula:



22. A pharmaceutical composition for preventing or alleviating damage to mammalian tissues comprising an amount of a compound of the following formula effective to decrease inflammation and free radical or oxidative damage in said tissues:



wherein:

A is a non-steroidal anti-inflammatory agent having a carboxylic moiety;

X is O or NR;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n'</sub>;

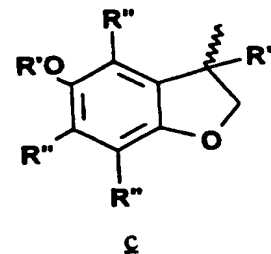
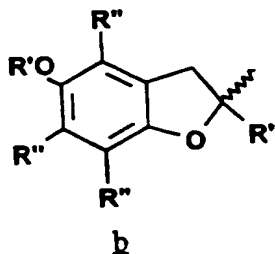
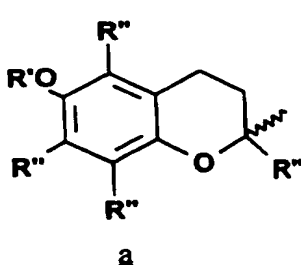
n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n'</sub>;

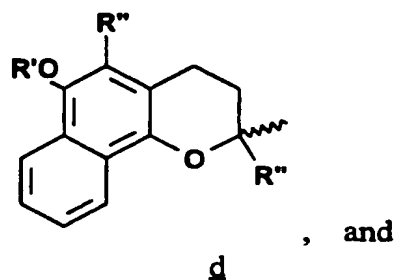
n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present;

n is 1 to 4 and m is 0 to 4 when Y is CH(OH);

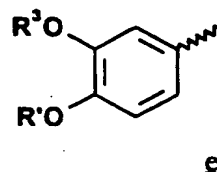
n' is 0 to 2; and

Z is selected from the group consisting of:





, and

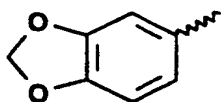


wherein:

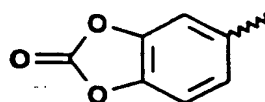
$R'$  and  $R^3$  are H,  $C(O)R$ ,  $C(O)N(R)_2$ ,  $PO_3^-$  or  $SO_3^-$ ;

$R''$  is H or  $C_1-C_6$  alkyl; and

$R'$  and  $R^3$  together may form a ring having the following formula:



or



provided that when Z is e, X is not O, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable vehicle therefore.

23. The composition according to Claim 22, wherein:

R is H or  $C_1-C_3$  alkyl;

Y is  $CH(OH)$ , m is 0 to 2, and n is 1 or 2, or Y is not present, m is 1 or 2, and n is 0 to 4;

Z is a, b, d or e;

$R'$  and  $R^3$  are H,  $C(O)CH_3$ ; and

$R''$  is  $CH_3$ .

24. The composition according to Claim 22, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: fenamic acids; indoles; phenylalkanoic acids; and phenylacetic acids.

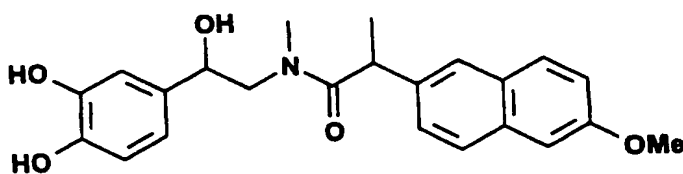
25. The composition according to Claim 22, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of:

loxoprofen; tolfenamic acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; acecloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; bromfenac; ketoprofen; fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen; ibuprofen; and diclofenac.

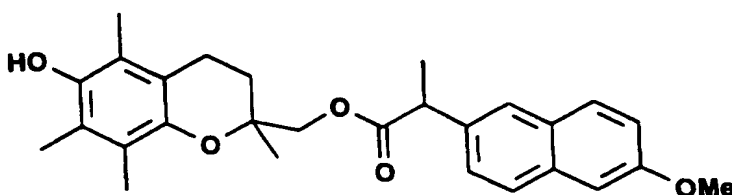
26. The composition according to Claim 22, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of naproxen, flurbiprofen and diclofenac.

27. The composition according to Claim 22, wherein the vehicle is a physiologically balanced irrigating solution.

28. The composition according to Claim 22, wherein the compound is selected from the group consisting of:

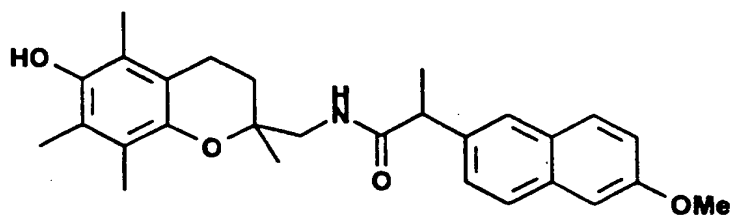


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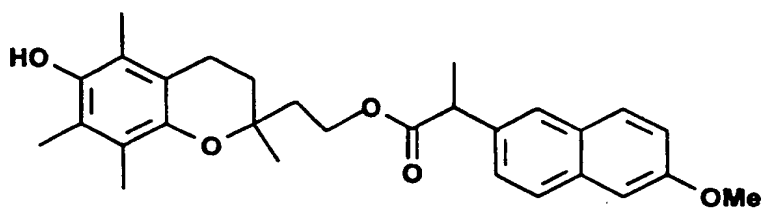


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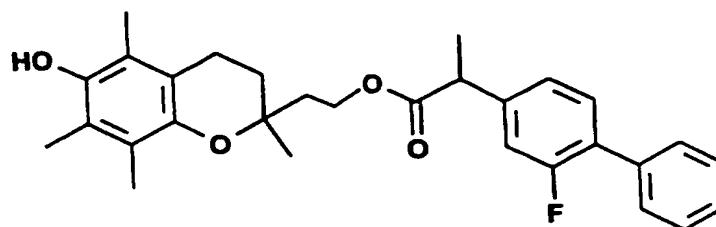
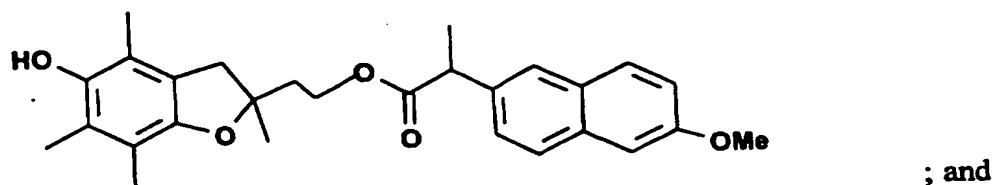
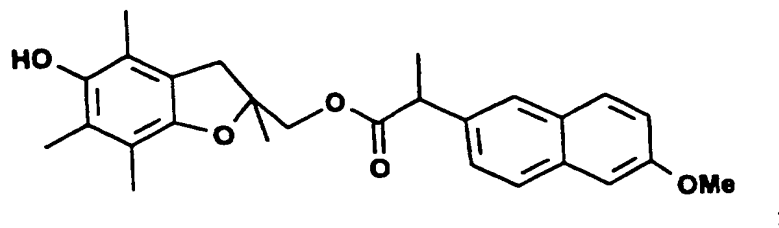




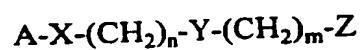
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29. A method of preventing or alleviating damage to mammalian tissues which comprises administering a therapeutically effective amount of a composition comprising an amount of a compound of the following formula effective to decrease inflammation and free radical or oxidative damage in said tissues:



wherein:

A is a non-steroidal anti-inflammatory agent having a carboxylic moiety;

X is O or NR;

R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n'</sub>;

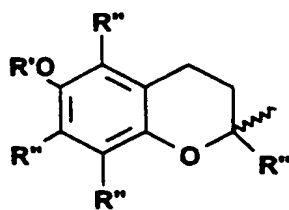
n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n'</sub>;

n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present;

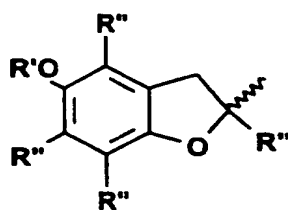
n is 1 to 4 and m is 0 to 4 when Y is CH(OH);

n' is 0 to 2; and

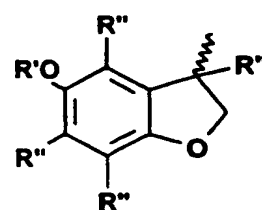
Z is selected from the group consisting of:



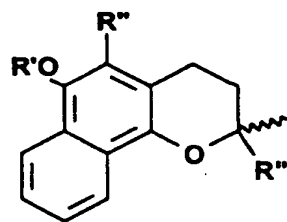
a



b

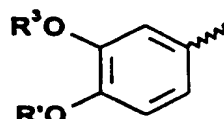


c



d

and



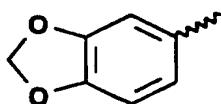
e

wherein:

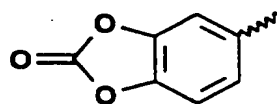
R' and R<sup>3</sup> are H, C(O)R, C(O)N(R)<sub>2</sub>, PO<sub>3</sub><sup>-</sup> or SO<sub>3</sub><sup>-</sup>;

R'' is H or C<sub>1</sub>-C<sub>6</sub> alkyl; and

R' and R<sup>3</sup> together may form a ring having the following formula:



or



;

provided that when Z is e, X is not O, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable vehicle thereof.

30. The method according to Claim 29, wherein the composition is administered to prevent or alleviate damage to ophthalmic tissues.

31. The method according to Claim 29, wherein:

R is H or C<sub>1</sub>-C<sub>3</sub> alkyl;

Y is CH(OH), m is 0 to 2, and n is 1 or 2, or Y is not present, m is 1 or 2, and n is 0 to 4;

Z is a, b, d or e;

10 R' and R<sup>3</sup> are H, C(O)CH<sub>3</sub>; and

R" is CH<sub>3</sub>.

32. The method according to Claim 29, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: fenamic acids; indoles; phenylalkanoic acids; and phenylacetic acids.

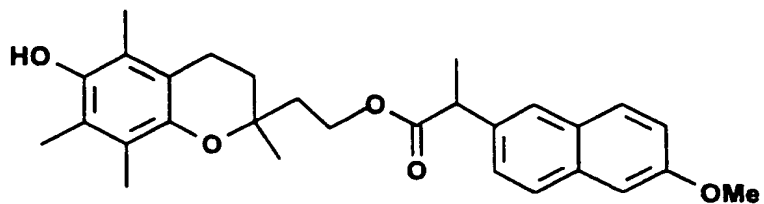
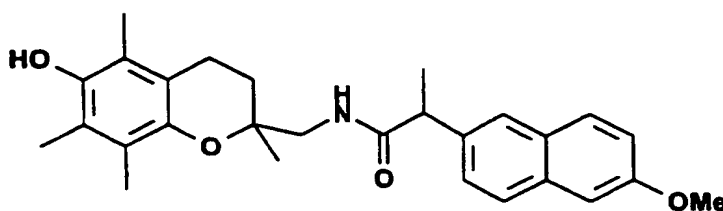
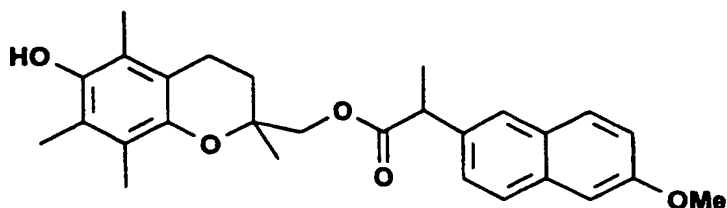
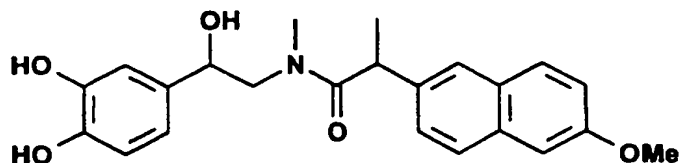
15 33. The method according to Claim 29, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of:

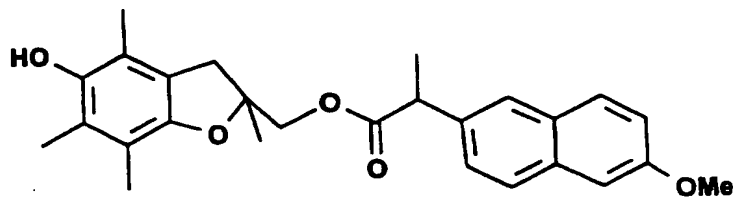
loxoprofen; tolfenamic acid; indoprofen; pirprofen; clidanac; fenoprofen; naproxen; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceloferac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; bromfenac; ketoprofen; 20 fenclofenac; alcofenac; orpanoxin; zomopirac; diflunisal; flufenamic acid; niflumic acid; mefenamic acid; pranoprofen; zaltoprofen; indomethacin; sulindac; tolmetin; suprofen; ketorolac; flurbiprofen; ibuprofen; and diclofenac.

34. The method according to Claim 29, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of naproxen, flurbiprofen and diclofenac.

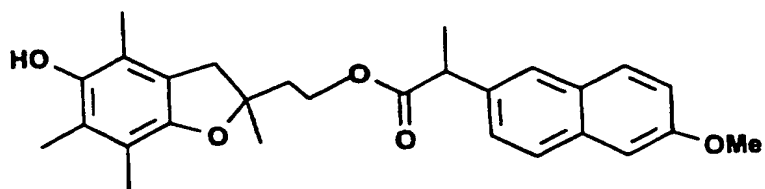
35. The method according to Claim 29, wherein the vehicle is a physiological balanced irrigating solution.

36. The method according to Claim 29, wherein the compound is selected from the group consisting of:

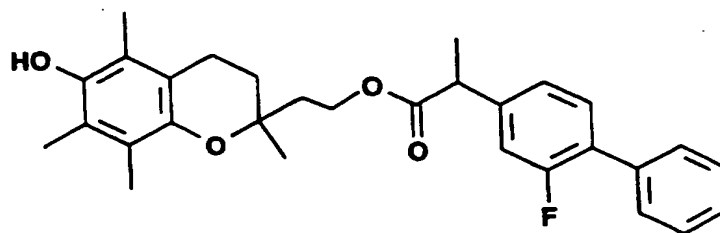




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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: <b>C07D 311/72, 307/80, C07C 235/34 A61K 31/355, 31/34, 31/16 // C07D 317/60, A61K 31/36</b>		A3	(11) International Publication Number: <b>WO 96/20187</b>
			(43) International Publication Date: 7 July 1996 (04.07.96)
(21) International Application Number: <b>PCT/US95/16779</b>		5610 Hunterwood Lane, Arlington, TX 76017 (US). NIXON, Jon, C. [US/US]; 1616 Hastings Drive, Mansfield, TX 76063 (US). GARNER, William, H. [US/US]; 1615 Heather Lane, Southlake, TX 76092 (US).  (74) Agents: MAYO, Michael, C. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  (81) Designated States: AU, BR, CA, CN, FI, JP, KR, MX, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>  (88) Date of publication of the international search report: 12 December 1996 (12.12.96)	
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(60) Parent Applications or Grants (63) Related by Continuation US 08/362,718 (CIP) Filed on 23 December 1994 (23.12.94) US 08/472,445 (CIP) Filed on 7 June 1995 (07.06.95)			
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(54) Title: ESTERS AND AMIDES OF NON-STEROIDAL ANTI-INFLAMMATORY CARBOXYLIC ACIDS WHICH MAY BE USED AS ANTI-OXIDANTS, 5-LIPOXYGENASE INHIBITORS AND NON-STEROIDAL ANTI-INFLAMMATORY PRODUCTS			
(57) Abstract			
<p>The compounds of the present invention are of the formula (I):  <math>A-X-(CH_2)_n-Y-(CH_2)_m-Z</math>          wherein: A is a non-steroidal anti-inflammatory agent (NSAIA); A-X is an ester or amide linkage derived from the carboxylic acid moiety of the NSAIA, wherein X is O or NR; R is H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl; Y, if present, is O, NR, C(R)<sub>2</sub>, CH(OH) or S(O)<sub>n</sub>; n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)<sub>n</sub>; n is 0 to 4 and m is 0 to 4 when Y is C(R)<sub>2</sub> or is not present; n is 1 to 4 and m is 0 to 4 when Y is CH(OH); n' is 0 to 2; and Z is (a), (b), (c), (d) or (e) wherein: R' and R<sup>3</sup> are H, C(O)R, C(O)N(R)<sub>2</sub>, PO<sub>3</sub>, or SO<sub>3</sub>; R' is H or C<sub>1</sub>-C<sub>6</sub> alkyl; and R' and R<sup>3</sup> together may form a ring having structure: (1) or (2); and provided that when Z is (e), X is not O. The compounds of the present invention also include pharmaceutically acceptable salts of the compounds of formula (I). Methods for treating inflammatory pathologies are disclosed. Particularly, the methods utilize pharmaceutical compositions containing certain compounds having an anti-inflammatory and anti-oxidant moiety covalently linked by an amide or ester bond. The compounds are useful in preventing and treating inflammatory disorders through several mechanisms.</p>			

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INTERNATIONAL SEARCH REPORT

Inten Application No  
PCT/US 95/16779

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D311/72 C07D307/80 C07C235/34 A61K31/355 A61K31/34  
A61K31/16 //C07D317/60, A61K31/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>DATABASE WPI Section Ch, Week 9551 Derwent Publications Ltd., London, GB; AN 95-403834 XP002009524 "New alkyl-hydroxy-benzofuran and derivatives - are 5-lipoxygenase inhibitors useful in allergy or inflammation e.g. bronchial asthma, rheumatic disease, psoriasis" see abstract &amp; WO,A,95 29906 (MEIJI MILK PRODUCTS CO., LTD.) 9 November 1995 see page 15</p>	1-4, 22-24
Y	<p>EP,A,0 183 869 (KURARAY CO., LTD.) 11 June 1986 see the whole document</p>	1,22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 October 1996

Date of mailing of the international search report

31.10.96

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Hartrampf, G

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 279 867 (EFEKA FRIEDRICH & KAUFMANN GMBH & CO KG) 31 August 1988 see the whole document ---	1,22
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 5, May 1989, pages 1006-1020, XP002009522 HAMMOND M.L. ET AL.: "2,3-Dihydro-5-benzofuranols as antioxidant-based inhibitors of leukotriene biosynthesis" see the whole document ---	1,22
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A	EP,A,0 387 771 (ONO PHARMACEUTICAL CO., LTD.) 19 September 1990 cited in the application see the whole document ---	1,22
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International Application No  
PCT/US 95/16779

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 4, 18 February 1994, pages 526-541, XP002015864 PEARCE B.C. ET AL.: "Inhibitors of cholesterol biosynthesis. 2. Hypocholesterolemic and antioxidant activities of benzopyran and tetrahydronaphthalene analogues of the tocotrienols" see the whole document	1,22
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A	--- EP,A,0 241 043 (WARNER-LAMBERT COMPANY) 14 October 1987 see claims 1,8,11	1-28
A	--- CHEMICAL & PHARMACEUTICAL BULLETIN , vol. 40, no. 2, 1992, pages 396-400, XP000570331 TSENG C.-F. ET AL.: "Inhibition of in vitro prostaglandin and leukotriene biosyntheses by cinnamoyl-.beta.-phenethylamine and N-acyldopamine derivatives" see page 398; table 2 -----	1-28

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/16779

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 29 to 36 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-14(all part.), 16-21, and 22-28(all part.)
2. Claims 1-14(all part.), and 22-27(all part.)
3. Claims 1-14(all part.), 15, and 22-28(all part.)

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
1-14(all part.), 16-21 and 22-28(all part.)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

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Information on patent family members

International Application No  
PCT/US 95/16779

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Information on patent family members

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